Original articles

A comparison of disease and gene frequencies of inborn errors of metabolism among different ethnic groups in the West Midlands, UK

A C J Hutchesson, S Bundey, M A Preece, S K Hall, A Green

Abstract

Objective—To assess birth and gene frequencies of specific autosomal recessively inborn errors of metabolism (IEM) within different ethnic groups.

Design—Retrospective study in a regional centre for investigation and treatment of IEM.

Subjects—All children born within the West Midlands NHS Region, UK, during the decade immediately preceding the 1991 National Census.

Methods—Birth frequencies for individual IEM were calculated separately for the main ethnic groups in the West Midlands using data from the West Midlands Neonatal Screening Programme, the regional register of IEM patients, and population frequencies from the National Census. Gene frequencies were calculated using previously documented observations on parental consanguinity rates and inbreeding coefficients.

Results—The overall incidence of recorded IEM was tenfold higher among Pakistanis compared to white children (1:318 v 1:3760), whereas only one AfroCaribbean child was identified (incidence 1:16 887). Tyrosinaemia type 1, cystinosis, mucopolysaccharidosis type 1, non-ketotic hyperglycinaemia, and hyperchylomicronaemia all occurred more frequently among Pakistanis. An increased gene frequency was only confirmed for tyrosinaemia. The incidence of phenylketonuria was similar in Pakistani and white children (1:14 452 v 1:12 611), but the gene frequency was significantly lower in Pakistanis (1:713 v 1:112). These results illustrate the interplay between gene frequency and parental consanguinity in determining disease frequencies in different populations, and indicate anticipated disease frequencies in the absence of consanguineous marriage. These figures have implications for the organisation of services for management of inborn errors, for genetic counselling, and for the assessment of gene flow in world populations.

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Inborn errors of metabolism (IEM) are an important cause of mortality and morbidity among children in developed countries. One characteristic of autosomal recessive IEM is their varying frequencies in different races, owing both to the past effects of natural selection, genetic drift, and migration and current influences, such as isolation and parental consanguinity. This is especially apparent in an ethnically and culturally diverse society such as that currently existing in parts of the United Kingdom (UK).

The distribution of different ethnic groups in the UK was assessed in a National Census in 1991,[1][2] and ethnic minorities form a significant proportion of the population of the cities of the West Midlands NHS Region. Within this region, the majority of children with IEM are investigated and managed through a single site, which since 1982 has maintained a register of all confirmed cases known there. We have used this register together with information from the Census to compare the frequencies of autosomal recessive IEM in different ethnic groups and to determine the extent to which the different disease incidences reflect the underlying gene frequencies.

Methods

The West Midlands Region, covering the counties of the West Midlands, Hereford and Worcester, Shropshire, Staffordshire, and Warwickshire, is the largest health region in England and Wales, with a population of 5 150 246. Residents of Pakistani descent form 1.9% of the total population, but are particularly concentrated in Birmingham, where they represent 6.9% of the total population. Residents of Indian descent represent 3.1% of the region's total population and 5.3% of the population of Birmingham. Within the Region, services for the diagnosis and treatment of IEM affecting amino acid, organic acid, and carbohydrate metabolism and lysosomal storage, including the neonatal screening service for detection of phenylketonuria (PKU) and congenital hypothyroidism at 6-10 days of age, are

Department of Clinical Chemistry, The Children's Hospital, Ladywood Middleway, Birmingham B16 8ET, UK
A C J Hutchesson
M A Preece
S K Hall
A Green

Clinical Genetics Unit, Birmingham Women's Hospital, Edgbaston, Birmingham B15 2TG, UK
S Bundey

Correspondence to:
Dr Hutchesson, Department of Clinical Chemistry, Royal Bolton Hospital, Minerva Road, Fairnworth, Bolton BL4 0RJ, UK.

Table 1 Births and frequency of inborn errors of metabolism affecting the major areas of amino acid, organic acid, and carbohydrate metabolism and storage disorders within the West Midlands in the decade preceding the 1991 National Census. (See text for explanation)

| | No of births (%) | Autosomal recessive inborn errors | |
		No of diagnoses (%)	Incidence (95% confidence intervals)
Total	707 720	263	1:2691 (1:2475–1:3037)
North west European	605 331 (85.5%)	160 (60.8%)	1:3783 (1:3240–1:4445)
Pakistani	28 903 (4.1%)	91 (34.6%)	1:318 (1:259–1:394)
Indian	31 062 (4.4%)	5 (1.9%)	1:6212 (1:2662–1:19 133)
AfroCaribbean	16 887 (2.4%)	1 (0.4%)	1:16 887 (1:3031–1:667 470)
Other/mixed race*	25 537 (3.6%)	6 (2.3%)	1:4256 (1:1955–1:11 598)

No of births is taken to be the number of neonates from whom a sample was collected for PKU screening at 6–10 days of age.
No data are available for the incidences of cystic fibrosis, sickle cell disease, or inherited endocrine diseases.
*This group includes those of other ethnic groups, those of mixed race, and those in whom data on ethnic origin was not available.

concentrated on a single site in the Department of Clinical Chemistry at the Children's Hospital, Birmingham. This department maintains a register of all confirmed diagnoses of IEM known there. The neonatal screening service (NNS) for the city of Birmingham differs from that for the rest of the Region. Firstly, all neonates are screened for sickle cell disease in addition to PKU, and the absence of haemoglobin A at this time is suggestive of β thalassaemia major or intermedia. Secondly, for historical reasons, the NNS programme for Birmingham uses heparinised plasma and tests for PKU by amino acid chromatography (as opposed to dried blood spots and the Guthrie microbiological assay for phenylalanine, used for the rest of the Region). This permits both visual inspection of plasma for lipaemia, and detection of some other aminoacidopathies.[3]

We assessed the incidence of autosomal recessive IEM among children born in the West Midlands in the decade preceding the 1991 National Census. The number of children screened during this period was obtained from Neonatal Screening Laboratory records, while their ethnicity as a percentage of the total was derived from Census data, using the number of children in each group resident in the region and aged under 10 years on the date of the Census (there is no documentation of paternal ethnicity and only voluntary documentation of maternal ethnicity at birth). The number of children with confirmed IEM born in the region during this period was derived from laboratory records, and their ethnicity from personal knowledge through involvement with clinical management. For each disease, the gene frequency q was calculated as the square root of the disease incidence D for white and Indian patients. This was inappropriate for the Pakistani children as 70% of marriages between Pakistani couples in the West Midlands are consanguineous,[4] and so for them we used the following formula, adapted from Dahlberg[5] and Edwards[6]:

$$D=i(Fq+(1-F)q^2)+(1-i)q^2$$

where i represents the proportion of consanguineous marriages and F the coefficient of inbreeding (70% and 0.0686 respectively in this population), the terms iFq and $i(1-F)q^2$ estimate the probability of homozygosity owing to descent and chance respectively in offspring of consanguineous partners, and the term

$(1-i)q^2$ indicates the probability of homozygosity in the rest of the population. The gene frequency q was obtained from this using the standard quadratic expansion:

$$q = \frac{-iF \pm \sqrt{(iF)^2 + 4(1-iF)D}}{2(1-iF)}$$

The disease frequency anticipated in the absence of consanguineous marriages (D_{corr}) was taken as q^2.

In addition to the number of affected children, the number of affected nuclear families (that is, those with one or more affected children born to the same parents) was noted. However, the former was used to calculate disease and gene frequencies in order to avoid biasing the results by any heterozygote couples who did not give birth to affected offspring.

For each disease, 95% confidence intervals (CI) for the number of cases observed were obtained from the Poisson distribution and used to calculate 95% CI for disease and gene frequencies. Where no cases were observed during the study period, a 95% CI (one sided) was obtained from the binomial distribution.

Results

During the 10 years immediately preceding the 1991 National Census, 707 720 children were born in the West Midlands. By January 1996, IEM with autosomal recessive inheritance affecting the major biochemical areas of amino acid, organic acid, and carbohydrate metabolism and mucopolysaccharide and other storage diseases had been diagnosed in 263 children born during this period. The total number of births and cases in different ethnic groups are shown in table 1. The majority of diagnoses were made in NW European and Pakistani children. Five Indian children were recorded, with type Ia and type II glycogen storage diseases, Niemann-Pick disease type C, steroid sulphatase deficiency, and Zellweger's syndrome. Seven other children were also identified, including two with PKU (one mixed Jordanian/European and one of AfroCaribbean and Arabic/Irish descent) and one each with argininaemia (Chinese), glycogen storage disease type II (AfroCaribbean), hyperoxaluria type 1 (East European), methylmalonic aciduria, and mucopolysaccharidosis type 1 (both of unrecorded ethnicity).

Table 2   Comparative disease and gene frequencies (95% confidence intervals) of the most common autosomal recessive inborn errors in the West Midlands region, in children born between 22 April 1981 and 21 April 1991

Disease	Cases (families)	Disease frequency		Gene frequency	
		NW European	Pakistani	NW European	Pakistani
Phenylketonuria	52 (50)	1:12 611 (1:9512–1:17 104)	1:14 452 (1:4001–1:119 337)	1:112 (1:98–1:131)	1:713 (1:210–1:5750)**
Tyrosinaemia type 1	13 (10)	1:302 665 (1:83 786–1:2.5×10⁶)	1:2628 (1:1468–1:5263)***	1:550 (1:289–1:1581)	1:144 (1:87–1:271)*
Galactosaemia	17 (15)	1:43 238 (1:25 770–1:79 085)	1:9634 (1:3297–1:46 716)	1:208 (1:161–1:281)	1:482 (1:176–1:2263)
Cystinosis	21 (20)	1:46 564 (1:27 230–1:87 476)	1:3613 (1:1834–1:8378)***	1:216 (1:165–1:296)	1:191 (1:105–1:421)
Hyperoxaluria type 1	5 (5)	1:201 777 (1:69 023–1:977 917)	1:14 552 (1:4001–1:119 337)*	1:550 (1:289–1:1581)	1:713 (1:210–1:5750)
MCADD	9 (9)	1:67 259 (1:35 430–1:147 089)	0 (<1:9350)	1:259 (1:188–1:384)	0 (<1:395)*
Mucopolysaccharidosis type 1	7 (6)	1:201 777 (1:69 044–1:978 391)	1:9634 (1:3297–1:46 716)**	1:449 (1:263–1:989)	1:482 (1:176–1:2263)
San Fillipo disease type C	8 (7)	1:86 476 (1:41 970–1:215 083)	1:9634 (1:3297–1:46 716)*	1:294 (1:205–1:464)	1:482 (1:176–1:2263)
Non-ketotic hyperglycinaemia	5 (5)	1:605 331 (1:108 646–1:2.4×10⁶)	1:7226 (1:2823–1:26 517)**	1:778 (1:330–1:4891)	1:366 (1:153–1:1293)
Niemann Pick disease type C	9 (7)	1:121 066 (1:51 875–1:372 855)	1:9634 (1:3297–1:46 716)*	1:348 (1:228–1:611)	1:482 (1:176–1:2263)

*p<0.05 v frequency in NW Europeans.
**p<0.01 v frequency in NW Europeans.
***p<0.001 v frequency in NW Europeans.
Other comparisons not significant.

Table 2 shows the number of cases and the disease and gene frequencies of specific IEM where information was available for the whole of the West Midlands, while table 3 shows the results for those diseases where information was only available for the city of Birmingham. The disease frequencies of tyrosinaemia type I and non-ketotic hyperglycinaemia (NKH) were approximately 100-fold greater among Pakistanis than among NW Europeans, while cystinosis, hyperoxaluria type I, and San Fillipo disease type C occurred approximately 10 times more frequently in Pakistanis than among NW Europeans. The gene frequency of tyrosinaemia type I was also significantly increased among Pakistanis, while that of cystinosis was similar among Pakistanis and NW Europeans.

The incidence of PKU was similar among Pakistanis and NW Europeans, but the gene frequency was significantly lower among Pakistanis. No cases of PKU were observed among Indians. Both the disease and gene frequency for galactosaemia were similar in both ethnic groups, but the significance of this is hard to evaluate as all affected Pakistani children were sibs from the same family.

If there were no intermarriage between relatives in the Pakistani population, the disease frequencies of PKU, tyrosinaemia, cystinosis, and galactosaemia predicted by these results would be respectively 1:508 740, 1:20 620, 1:36 480, and 1:224 600. Among rarer conditions, the anticipated disease frequency of hyperoxaluria type 1 would be 1:508 370 and that of non-ketotic hyperglycinaemia 1:134 000. The relative increase D/D_{corr} in the frequency of

Table 3   Disease and gene frequencies (95% confidence intervals) of two autosomal recessive diseases in Birmingham, in children born between 22 April 1981 and 21 April 1991

	Hyperchylomicronaemia	β thalassaemia
No of cases (families)	6 (4)	23 (20)
Disease frequency		
NW European	0 (<1:30 976)	0 (<1:30 976)
Pakistani	1:3386 (1:1556–1:9228)**	1:1355 (1:821–1:2420)**
Indian	0 (<1:3003)	1:2216 (1:949–1:6824)**
Gene frequency		
NW European	0 (<1:176)	0 (<1:176)
Pakistani	1:180 (1:123–1:650)	1:81 (1:53–1:132)**
Indian	0 (<1:55)	1:47 (1:31–1:83)**

**p<0.01 v frequency in NW Europeans.
Other comparisons not significant.

each condition followed the equation $D/D_{corr}=1.84 + (0.002/D)$.

Within Birmingham, hyperchylomicronaemia (hyperlipidaemia type I) was detected in six Pakistani children (plasma triglycerides of between 13 and >200 mmol/l at neonatal screening, median 60 mmol/l) and none from other ethnic groups. The incidence of hyperchylomicronaemia was significantly increased among Pakistanis (1:3386, p<0.01 v NW Europeans), but the total number of births was too low to permit firm conclusions to be drawn about comparative gene frequencies in different ethnic groups. If intermarriage between relatives did not occur, the anticipated incidence in the Pakistani population would be 1:32 400.

We also assessed the disease frequency of three common X linked recessive inborn errors, adrenoleucodystrophy, Menkes disease, and ornithine transcarbamylase deficiency. Twelve affected children (five, three, and four respectively) were identified in the West Midlands, only one of whom was derived from an ethnic minority group (an Indian child with ornithine transcarbamylase deficiency). This number of cases did not permit any comparison of disease frequencies in different ethnic groups.

Discussion

This study confirms that the incidence of IEM with autosomal recessive inheritance is approximately 10 times greater among the UK Pakistani population than among NW Europeans. We have also been able to estimate both the disease incidences and the gene frequencies for certain specific IEM, and to show an increase in the frequencies of individual diseases by between five- and 35-fold in the Pakistani community compared to those predicted in the absence of intermarriage between relatives.

We have previously shown that the disease frequency of tyrosinaemia type I is increased in Pakistanis compared to NW Europeans.[3] This work indicates this is both because of the effect of consanguinity, in increasing the anticipated disease frequency eightfold, and an increased gene frequency. Other workers have suggested that a common causative mutation may be present in the Pakistani population.[7] It is also

possible that the gene frequency for hyperchylomicronaemia may be increased in this group. Although the number of births in Birmingham was too low to permit confirmation of this, the estimated world wide incidence of 1-1.5 per million[8] would suggest an overall gene frequency of 1:820-1000, compared to the gene frequency we calculated in Pakistanis of 1:180. In contrast, the gene frequency for PKU appears lower among Pakistanis than among NW Europeans, but the effect of consanguinity is to increase the disease frequency in Pakistanis by a factor of 35 to attain that seen among Europeans. Several other conditions, such as cystinosis and non-ketotic hyperglycinaemia, also show an increased disease incidence among the Pakistani population; for cystinosis, the gene frequency appeared similar among Pakistanis and Europeans, while the incidence of other conditions was too low to draw any conclusions about comparative gene frequencies.

Our identification of births through the neonatal screening laboratory may have led to a slight underestimate of the total birth rate. Although we have included the small number of children whose parents declined neonatal screening, we are unable to identify those who died before collection of the neonatal screening sample. In view of the current low perinatal mortality rate, the error introduced by this is likely to be insignificant. We are also unable to identify any children (excluding those with PKU) who were born after 21 April 1981 and died before establishment of the IEM register in 1982. Those surviving after this date, even if diagnosed before, have been included because of involvement of the laboratory with biochemical monitoring and clinical management. Again, we believe the number of such children is likely to be small; to illustrate this, only six children with PKU were born within this period. Most importantly, some children with inborn errors may have died without recognition of the underlying diagnosis. This latter applies especially to tyrosinaemia, NKH, and disorders of fat oxidation such as medium chain acyl-CoA dehydrogenase deficiency (MCADD), which can (and in the case of NKH usually does) present with neonatal death. As a special interest in tyrosinaemia exists within this unit, we doubt that many cases have been overlooked. We know of only one such child, who died aged 2 days.[3] However, we suggest it is important to consider the possibility of inborn errors of metabolism in neonates with severe illness, and that tyrosinaemia and NKH merit particular consideration in Pakistani children.

It is also possible that some children may have failed as yet to present clinically. MCADD, for example, is thought to be widely underdiagnosed. Thus, while the gene frequency observed here in NW Europeans was 1:259, a recent neonatal screening survey in the West Midlands found an overall frequency for the common causative A985G mutation of 1:104.[9] We did observe a significantly lower gene frequency among Pakistani children, which agrees with the rarity of this diagnosis outside those of NW European ethnicity.[10] In

contrast to the situation with MCADD, detection of PKU (through the national neonatal screening programme) is thought to approach 100%. Hyperchylomicronaemia may present as an incidental finding, but the degree of lipaemia (median plasma triglycerides of 60 mmol/l) observed at neonatal screening suggests that few affected children born in Birmingham remain undetected. Of the other diseases studied, tyrosinaemia, galactosaemia, β thalassaemia, and cystinosis usually present in the first few years of life. Some children with these disorders may have been both diagnosed and managed in other hospitals. No requirement exists for such children to be reported to the Children's Hospital, Birmingham for inclusion on the IEM database, and they would therefore not be included in this survey. The number of such children, whose care is delivered totally through either a district general hospital or a supraregional centre, and with whom the Children's Hospital, Birmingham has never had any involvement either at the clinical or laboratory level, is likely to be small. This is especially true for tyrosinaemia and other IEM affecting the liver, as the Children's Hospital is a supraregional centre for the medical and surgical management of paediatric liver disease.

In order to define the ethnicity of the population in the West Midlands, we have confined this study to those born within the 1980s. Laboratory services for the diagnosis of certain disorders (for example, those of purine and pyrimidine metabolism) were not fully established during this period, and some diagnoses may have been missed as a result. Although this may have led to an artefactually low figure for total diagnoses, we see no reason to suppose that any ethnic group would be particularly affected.

This study has treated Europeans as a homogeneous group in which consanguineous marriages are absent. This simplification may be invalid, particularly in the case of galactosaemia, in which three children belonged to an extensively inbred Irish travelling family. In other diseases, consanguineous marriages among NW Europeans were rare.

One AfroCaribbean child with glycogen storage disease type 2, and one of mixed AfroCaribbean/Arabic origin with PKU, were identified. The incidence of autosomal recessive IEM (excluding sickle cell disease) in AfroCaribbean children was significantly lower than that in the total population, and this group has been noted to be under-represented in local genetic clinics.[11] However, the size of the AfroCaribbean population in the West Midlands was too low for the incidence of IEM in this group to be compared with that in NW Europeans.

These results confirm previous observations that single gene disorders occur with increased frequency among the Pakistani population, in comparison both to NW Europeans and to Indians, who may be expected to share a more similar gene pool. Indeed, although only 5% of the population studied were of Pakistani descent, they accounted for about a third of

patients with autosomal recessive IEM. This appears to be the result of the effect of inbreeding, acting on the background of differences in gene frequency. Thus, the gene frequency of PKU is much lower among Pakistanis than among Europeans, but the disease incidence is similar in both groups. For cystinosis, the gene frequency appears similar in the two groups, but the disease incidence is higher among Pakistanis. The attendance of Pakistanis at regional genetic clinics is relatively low,[11] and it has been suggested that their awareness of genetic conditions, and the amount of educational material available to them, is inadequate.[12] Darr[13] found that unsympathetic genetic counselling, notably with regard to consanguineous marriages, was counterproductive and could lead to confusion, but that families with an affected child remained open to counselling and responded well to an approach that took due account of cultural practices. Linguistic difficulties may also limit understanding of genetic issues.[14] Roberts *et al*[11] noted that attendance of Pakistanis at a genetic clinic increased if it was known that a Pakistani (female) doctor would also be present, which could be attributable to increased confidence in understanding both of language and of culture. Following that work, a Pakistani Muslim doctor has participated in the genetic clinics held by one of us (SB), and a Muslim fieldworker has been appointed to initiate an education programme and help in genetic clinics. We would also recommend the availability of leaflets in Urdu and other appropriate languages on genetic counselling, recessive diseases, and consanguinity.

Finally, we would like to encourage documentation of both ethnicity and the family tree in the records of all patients with IEM. Data on ethnicity is considered important by NHS administrators for the purpose of auditing their service, but is equally important for those involved in the care of patients and in the genetic counselling of their relatives and is also valuable in monitoring patterns of disease within the community.

1 Office of Population Censuses and Surveys. *The 1991 Census County Report: West Midlands (Series CEN 91 CR 43)*. London: HMSO, 1992.
2 Office of Population Censuses and Surveys. *The 1991 Census Report for England: Regional Health Authorities (Series CEN 91 RERHA)*. London: HMSO, 1993.
3 Hutchesson ACJ, Hall SK, Preece MA, Green A. Neonatal screening for tyrosinaemia. *Arch Dis Child* 1996;74:F191-4.
4 Bundey S, Alam H. A five-year prospective study of the health of children in different ethnic groups, with particular reference to the effects of inbreeding. *Eur J Hum Genet* 1993;1:206-19.
5 Dahlberg G. Inzucht bei Polyhybridat beim Menschen. *Hereditas* 1930;14:83-96.
6 Edwards JH. Familiarity, recessivity and germline mosaicism. *Ann Hum Genet* 1989;53:33-47.
7 Rootwelt H, Berger R, Gray G, Kelly DA, Coskun T, Kvittingen EA. Novel splice, missense, and nonsense mutations in the fumarylacetoacetase gene causing tyrosinemia type I. *Am J Hum Genet* 1994;55:653-8.
8 Brunzell JD. Familial lipoprotein lipase deficiency and other causes of the chylomicronemia syndrome. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic and molecular bases of inherited disease*. 7th ed. New York: McGraw-Hill, 1995:1913-32.
9 Seddon HR, Green A, Gray RGF, Leonard JV, Pollitt RJ. Regional variations in medium-chain acyl-CoA dehydrogenase deficiency. *Lancet* 1995;345:135-6.
10 Roe CR, Coates PM. Mitochondrial fatty acid oxidation disorders. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic and molecular bases of inherited disease*. 7th ed. New York: McGraw-Hill, 1995:1501-33.
11 Roberts A, Cullen R, Bundey S. The representation of ethnic minorities at genetic clinics in Birmingham. *J Med Genet* 1996;33:56-8.
12 Lawry S. *Thalassaemia - access to appropriate screening and counselling care for Muslims of Pakistani origin in Oxford*. Dissertation submitted for BSc (Hons) in Anthropology and Geography. Oxford: Oxford Brookes University, 1993.
13 Darr A. *The social implications of thalassaemia among Muslims of Pakistani origin in England - family experience and service delivery*. PhD thesis, University of London, 1991.
14 Mehta L, Young ID. Attitudes of Asian families to genetic counselling. *J Med Genet* 1985;22:413.